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(71) Applicant *(for all designated States except US)*: **NICOX S.A.** [FR/FR]; 2455, route des Dolines, Espace Gaia II - Bâtiment I, F-06906 Sophia Antipolis Cedex (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TRESPIDI, Laura** [IT/IT]; Via Lungo Adda, 56, I-26026 Pizzighettone (IT). **DEL SOLDATO, Piero** [IT/IT]; Via Toti, 22, I-20052 Monza (IT).

(74) Agent: **GERVASI, Gemma**; Notarbartolo & Gervasi S.p.A., Corso dei Porta Vittoria, 9, I-20122 Milano (IT).

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WO 02/051385 A1

(54) Title: SOLID DISPERSIONS OF NITRATE ACTIVE PRINCIPLES

(57) Abstract: The invention relates to solid dispersions of nitrate active principles in at least one polymer chosen from the group consisting of polyvinyl pyrrolidone, cellulose derivatives or polyethylene glycol, their production processes and pharmaceutical formulations including said dispersions.

**Solid dispersions of nitrate active principle**

FIELD OF THE INVENTION

The present invention relates to solid dispersions of nitrate active principles characterized by an increased dissolution rate and/or apparent solubility of said active principles and to a method for their production.

STATE OF THE ART

The applicant has developed a number of active principles, characterized by the presence in their structure of a nitro group, having remarkably advantageous pharmacological properties. These active principles are described in the patents: EP670825, EP722434, EP759899, EP609415, US5703073, and in the patent applications WO98/15568, WO98/21193, WO00/51988, WO00/61537, WO00/61541, WO00/61604, WO00/25776, MI99A001817.

Unfortunately, the utility of many of the above mentioned active ingredients is limited by their scarce solubility in water, which results in an insufficient and irregular absorption and a slow onset of the pharmacological action. This last aspect is particularly problematic in case of active ingredients such as, for instance, antinflammatory active ingredients and/or analgesics for which a rapid onset of the therapeutic action is of fundamental importance.

Thus, there is as need to develop new pharmaceutical formulations for the administration of nitrate active principles which, compared with traditional formulations, are characterized by an improved bioavailability and a faster onset of action.

It is known that the dissolution rate of poor water-soluble drugs can be increased by their conversion to the corresponding amorphous forms. A technique which can be used to this purpose is the formation of a solid dispersion of the active agent in an inert matrix, usually of polymeric nature. Nevertheless, this technique does not always allow to obtain the amorphous form and consequently the increase in dissolution rate of the active agent. Several parameters such as, for instance the interactions between the polymer and the active ingredient, the ratio between then and the production technique adopted influence the chemical-physical features of the solid dispersion obtained. Thus, for each particular active ingredient it is necessary to select both the polymer and the operative conditions for the preparation of the dispersion that lead to the conversion to the amorphous form.

SUMMARY OF THE INVENTION

The inventors have now found that it is possible to obtain an increase in the dissolution rate and/or the apparent solubility and consequently in the bioavailability of nitrate active principles by forming solid dispersions of said active principles characterized in that the inert matrix includes at least one polymer chosen among polyvinyl pyrrolidone, cellulose ethers and polyethylene glycols.

Therefore, the present invention refers to solid dispersions comprising at least one nitrate active principle and a hydrophilic polymer chosen among polyvinyl pyrrolidone, cellulose ethers and polyethylene glycols.

DESCRIPTION OF THE FIGURES

Figures 1, 2 and 3 show the thermograms of the crystalline form and of the amorphous solid dispersion according to the present invention of the following derivatives:

4- acetylaminophenyl ester of 4 nitroxybutanoic acid (NCX701)

2- (acetyloxy-benzoic-acid-3-nitroxymethyl) phenyl ester (NCX 4016)

(hydroxycortisone 21-[(4'nitroxymethyl)benzoate] (NCX 1022)

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to solid dispersions comprising at least one nitrate active ingredient and a hydrophilic polymer chosen among polyvinyl pyrrolidone, preferably having a molecular weight comprised between that of the polyvinyl pyrrolidone K17 and that of polyvinilpyrrolidone K30, cellulose ethers and polyethylene glycol, preferably having a molecular weight higher than that of PEG 1000, and more preferably PEG with a molecular weight higher than that of PEG 1500 and lower than that of PEG 6000. Among the cellulose ethers particularly preferred is the hydroxypropylmethylcellulose, preferably having a viscosity at 20°C, in a 2% aqueous solution, lower than 50 cPs, and preferably hydroxypropylmethylcellulose with viscosity comprised between 5 and 50 cPs.

By "nitrate active principles" it is meant compounds having formula (I).

$$A\text{-}X_1\text{-}L\text{-}(W)_p\text{-}NO_q \qquad (I)$$

wherein:

**p** is an integer equal to 1 or 0;

**q** is an integer equal to 1 or 2;

**A=R-$T_1$-**, wherein **R** is the radical of a pro-drug having formula **R-$T_1$-Z**, chosen among the therapeutic classes of drugs reported here after, wherein

**Z** is **H, OH, $NH_2$, $NHR_3$, $N(R_3)_2$**, wherein $R_3$ is a linear or branched $C_1$-$C_5$ alkyl radical

**$T_1$ = $(CO)_t$** or **$(X)_{t'}$**, wherein X = an oxygen atom, a sulphur atom or $NR_2$ wherein $R_2$ is hydrogen or a linear or branched alkyl, having from 1 to 5 carbon atoms, t and t' are integer and equal to zero or 1, provided that t = 1 when t' = 0; t = 0 when t' = 1;

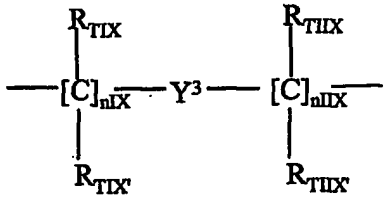
**$X_1$ = -$T_B$-Y-$T_{BI}$** wherein $T_B$ and $T_{BI}$ are the same or different

**$T_B$ = (CO)** when t = 0, **$T_B$ = X** when t' = 0, being X as above defined;

**$T_{BI}$ = $(CO)_{tx}$** or **$(X)_{txx}$** wherein tx and txx are 0 or 1; with the proviso that tx = 1 when txx = 0; tx = 0 when txx = 1; X is as above defined;

Y is a bivalent bridging group chosen among the following:

**1)**



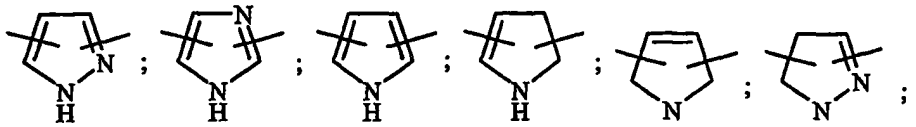

wherein:

**nIX** is an integer comprised between 0 and 3, preferably 1;

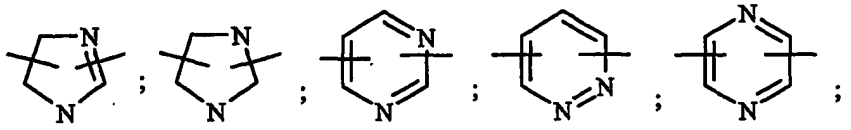
**nIIX** is an integer comprised between 1 and 3, preferably 1;

$R_{TIX}$, $R_{TIX'}$, $R_{TIIX}$, $R_{TIIX'}$, equal or different from one another, are H or linear or branched $C_1$-$C_4$ alkyl; preferably $R_{TIX}$, $R_{TIX'}$, $R_{TIIX}$, $R_{TIIX'}$ are H.

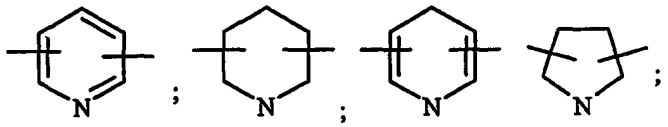
**$Y^3$** is a saturated , unsaturated or aromatic heterocyclic ring having 5 or 6 atoms and containing one or two nitrogen atoms, $Y^3$ is preferably chosen among the following bivalent radical:



(Y1) (Y2) (Y3) (Y4) (Y5) (Y6)



(Y7) (Y8) (Y9) (Y10) (Y11)



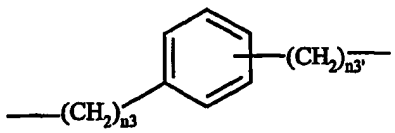
(Y12) (Y13) (Y14) (Y15)

wherein (Y12) is preferred ;

**2)** an alkylene group R' wherein R' is $C_1$-$C_{20}$ linear or branched when possible, having preferably 2 to 6 carbon atoms, optionally substituted with at least one of the following groups: $-NH_2$, -OH or $-NHCOR_3$, wherein $R_3$ is a linear or branched $C_{1-5}$ alkyl;

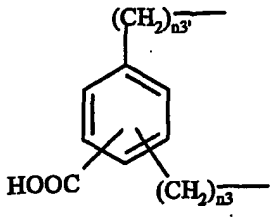
**3)** a cycloalkylene having from 5 to 7 carbon atoms, optionally substituted with side chains R', wherein R' is as defined above, and at least one carbon atom of the cycloalkylenic ring can be optionally substituted with etheroatoms.

**4)**



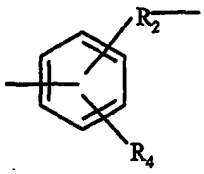
wherein n3 is an integer from 0 to 3 and n3' is an integer from 1 to 3;

**5)**



wherein n3 and n3' have the above indicated meaning,

6)

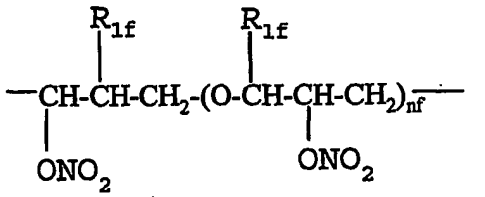


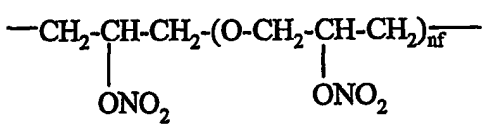
wherein

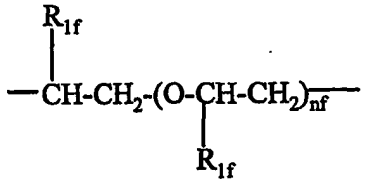
$R_4$ is hydroxy, hydrogen, alkoxy $R_5O$- wherein $R_5$ is a linear, branched or cyclic $C_{1-10}$ alkyl group, preferably $R_5$ is a methyl group;

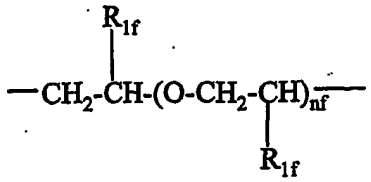
$R_2$ is a linear or branched $C_2$-$C_{10}$ alkenyl group, including at least one double bond, preferably $R_2$ is the ethenylene group (-CH=CH-);

7)









wherein $R_{1f}$ = H, $CH_3$ and nf is an integer from 0 to 6; preferably from1 to 4;

8) or Y is the bivalent radical whose pr cursor Z-$T_B$-Y-$T_{BI}$-Z, wherein Z is as defined above and it is chosen among the following compounds:

aspartic acid, histidine, 5-hydroxytryptophan, 2-thiouracil, 2-mercaptoethanol, hesperidine, secalcipherol, 1-α-OH-Vitamin D2, flocalcitriol, 22-oxacalcitriol, 24,28-

methylen-1α-hydroxyvitamin D2, succinic acid, L-carnosine, anserine, selenocysteine, selenomethionine, penicillamine, N-acetylpenicillamine, cysteine, N-acetylcysteine, glutathione, gallic acid, ferulic acid, gentisic acid, citric acid, caffeic acid, hydrocaffeic acid, p-coumaric acid, vanillic acid, chlorogenic acid, kynureic acid, siringic acid, nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulfuretin, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductic acid, methoxyhydroquinone, hydrohydroxyquinone, propyl gallate, saccharose, 3,5-di-ter-butyl-4-hydroxybenzyl-thioglycolate, allopurinol, conyferyl alcohol, 4-hydroxyphenethyl alcohol, p-coumaric alcohol, curcumin, N,N'-diphenyl-p-phenylenediamine, thionine, hydroxyurea, 3,3'-thiodipronic acid, fumaric acid, dihydroxymaleic acid, N-methylendiethanolamine, thiodiethylenglycol, 1,4-dioxane-2,6-dimethane, tetrahydropyran-2,6-di-methanol, 4H-pyran-2,6-di-methanol, cyclohexene-1,5-dimethanol, 1,4-dithian-2,6-dimethanol, thiophene-2,5-di-methanol, oxazole-2,5-di-methanol.

**L**= covalent bond, or **L = X**, **X** being as defined above, **L = (CO)**

**W = $Y_T$-X-** wherein **$Y_T$** has the same meanings of **Y**, but is different from **Y**,

**R-$T_1$-Z** is chosen among the following drugs:

- Non steroidal anti-inflammatory drugs: aceclofenac, acemetacin, acetylsalicylic acid, alclofenac, alminoprofen, amfenac, ampiroxicam, balsalazide, bendazac, bermoprofen, α-bisabolol, bromfenac, bromosaligenin, bucloxic acid, butibufen, carprofen, cinmetacin, clidanac, clopirac, diclofenac, CS-670, diflunisal, ditazol, enfenamic acid, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentiazac, fepradinol, flufenamic acid, flunixin, flunoxaprofen, flurbiprofen, glucametacin, glycol salicylate, ibuprofen, ibuproxam, indomethacin, indoprofen, isofezolac, isoxepac, isoxicam, ketoprofen, ketorolac, lornoxicam, loxoprofen, mechlofenamic acid, mefenamic acid, meloxicam, mesalamine, metiazinic acid, mofezolac, naproxen, niflumic acid, olsalazine, oxaceprol, oxaprozin, oxifenbutazone, parsalmide, pemedolac, perisoxal, phenyl acetylsalicilate, pirazolac, piroxicam, pirprofen, pranoprofen, protizinic acid, salacetamide, salicylamido-O-acetic acid, saliciylsulforic acid, salsalate, sulindac, suprofen, suxibuzone, tenidap, tenoxicam, thiaprofenic acid, thiaramide, tinoridine, tolfenamic acid, tolmetin, tropesin, xenbucin, ximoprofen, zaltoprofen, zom pi-

rac, tomoxiprol,

Analgesics: paracetamol, acetaminosalol, aminochlorthenoxazin, acetylsalicilic acid, 2-amino-4-picoline, acetylsalicylsalicilyc acid, anileridine, benoxaprofen, benzylmorphine, 5-bromosaliciylic acid acetate, bucetin, buprenorfine, butorfanol, capsaicin, cincofenol, ciramadol, clometacine, clonixin, codeine, desomorphine, dezocine, dihydrocodeine, dihydromorphine, dimefeptanol, dipyrocetyl, eptazocine, etoxazen, ethylmorphine, eugenol, floctafenine, fosfosal, glafenine, hydrocodon, hydromorone, hydroxypetidine, ibufenac, p-lactophenetide, levorfanol, meptazinol, metazocine, metopon, morphine, nalbuphine, nicomorphine, norlevorfanol, normorphine, oxycodone, oxymorphon, pentazocine, fenazocine, fenocoll, fenoperidine, fenilbutazone, phenylsalicylate, phenilramidol, salicin, salicylamide, tiorphan, tramadol, diacereine, actarit;

- Steroids: chenodeoxycholic acid, ursodeoxycholic acid, alclomethasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chlorprednisone, clobetasol, clobethasone, clocortolone, cloprednol, corticosteron, cortisone, cortivazol, deflazacort, desonide, desoximethasone, dexamethasone, diflorasone, diflucortolone, difluprednate, estradiol, ethynilestradiol, fluazacort, flucloronide, flucortyn butyl, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halomethasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, mestranol, metilprednisolone, mitatrienediol, mometasone furoate, moxestrol, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylaminoacetate, prednisone, prednival, prednylidene, rimexolone, 21-acetoxy-pregnenolone, triamcinolone hexacetonide, triamcinolone acetonide, triamcinolone, tixocortol;
- Bronchodilatory drugs: acephilline, albuterol, bambuterol, bamiphylline, bevonium methyl sulfate, bitolterol, carbuterol, clenbuterol, clorprenaline, dioxetedrine, diphylline, ephedrine, epinephrine, eprozinol, etaphedrine, ethylnorepinephrine, etophylline, fenoterol, flutoprium bromide, hexoprenaline, ipratropium bromide, isoetarine, isoprotenerol, mabuterol, metaprotenerol, oxitropium bro-

mide, pirbuterol, procaterol, protokylol, proxyphylline, reproterol, rimiterol, salmeterol, soterenol, terbutaline, 1-theobromoacetic acid, thiotropium bromide, tretoquinolol, tulobuterol, oxybutinyn, zaprinast.

- Expectorants and mucolitic agents: ambroxol, bromexine, domiodol, erdosteine, guaiacol, guaifenesine, glycerol iodurate, letosteine, mesna, sobrerol, stepronin, terpin, thiopronin;
- Anti-asthmatic, antiallergic and antihistaminic drugs: acrivastine, alloclamide, amlexanox, cetirizine, clobenzepam, chromoglycate, chromolyn, epinastine, fexofenadine, formoterol, hystamine, hydroxyzine, levocabastine, lodoxamide, mabuterol, metron s, montelukast, nedocromil, repirinast, seratrodast, suplatast tosylate, terfenadine, tiaramide, bromexine, formoterol;
- ACE-inhibitors: alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, losartan, moveltipril, naftopidil, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, urapidil;
- β-blockers: acebutolol, alprenolol, amosulalol, arotinolol, atenolol, betaxolol, bevantolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, dilevalol, epanolol, esmolol, indenolol, labetalol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipridalol, oxprenolol, penbutolol, pindolol, practolol, pronetalol, propranolol, sotalolol, sulfinalolol, talinolol, tertatolol, tilisolol, timolol, toliprolol, xibenolol;
- Drugs for vascular disorders: acetorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil hemisuccinate, benziodarone, betaistine, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, heparine, dalteparin, dipiradamol, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isbogrel, isoxsuprine, lamifiban, nadroparin, nicotinoyl alcohol, nylidrin, ozagrel, perhexiline, prenilamine, papaveroline, reviparin sodium salt, ridogrel, suloctidil, tinophedrine, tinzaparin, triflusal, xanthinol niacinate, fenilpropanolamine, midodrine;
- Antidiabetics: acarbose, carbutamide, glibornuride glybuthiazol, miglitol, repaglinide, troglitazone, 1-buthyl-3-methanyl-urea, tolrestat, nicotinamide;
- Antitumoral drugs: ancitabine, anthramicine, azacitidine, azaserine, 6-azauridi-

ne, bicalutamide, carubicine, carzinophilin, chlorambucil, chlorozotocin, citarabine, daunorubicine, defosfamide, demecolcine, denopterine, 6-diazo-5-oxo-L-norleucine, docetaxel, doxifluridine, doxorubicine, droloxifene, edatrexate, eflornithine, enocitabine, epirubicine, epitiostanol, etanidazole, etoposide, fenretinide, fludarabine, fluorouracyl, gemcitabine, hexestrol, idarubicine, lonidamine, mannomustine, melphalan, menogaril, 6-mercaptopurine, methotrexate, mitobronitol, mitolactol, mitomycins, mitoxantrone, mopidamol, micophenolic acid, ninopterine, nogalamycin, paclitaxel, pentostatin, pirarubicin, piritrexim, plicamicine, podofillic acid, porfimer sodium, porfiromycin, propagermanium, puromycin, ranimustine, retinoic acid, roquinimex, streptonigrin, streptozocin, teniposide, tenuazonic acid, tiamiprine, thioguanine, tomudex, topotecan, trimetrexate, tubercidin, ubenimex, vinblastine, vincristine, vindesine, vinorelbine, zorubicine;

- Antiulcer drugs: ε-acetamidocaproic acid, arbaprostil, cetraxate, cimetidine, ecabet, enprostil, esaprazole, irsogladine, misoprostol, omeprazol, ornoprostil, pantoprazol, plaunotol, rioprostil, rosaprostol, rotraxate, sofalcone, trimoprostil;
- Antihyperlipidemic drugs: atorvastatine, cilastatine, dermostatine, fluvastatine, lovastatine, mevastatine, nistatine, pentostatine, pepstatine, privastatine sodium salt, simvastatine;
- Antibacterial drugs: amdinocillin, amoxicillin, ampicillin, apalcillin, apicyclin, aspoxicillin, azidamfenicol, azidocillin, azlocillin, aztreonam, benzoylpas, benzyl penicillinic acid, biapenem, bicozamycin, capreomycin, carbenicillin, carindacillin, carumonam, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazoline, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, cefoxanide, cefotaxime, cefotetan, cefotiam, cefoxitin, cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephacetrile sodium, cephalexin, cephaloglycin, cephaloridine, cephalosporin C, cephalothin, cephapirin sodium, cephradine, chloramphenicol, chlortetracicline, cinoxacine, clavulanic acid, clofoctol, clometocilline, cloxacilline, cyclacilline, cycloserine, demeclocicline, dicloxacillin, epicillin, fenbecillin, flomoxef, floxacillin, hetacillin, imipenem, lenampicillin, loracarbef, lymecycline, mafenide, me-

clocycline, meropenem, metampicillin, metacicline, meticillin sodium salt, mezlocillin, minocicline, moxalactam, mupirocin, myxin, negamycine, novobiocin, oxacillin, pamipenem, penicillin G potassium salt, penicillin N, penicillin O, penicillin V, pheneticillin potassium salt, pipaciclyne, piperacillin, pirlimycin, porfiromycin, propicillin, quinacillin, ritipenem, rolitetracycline, sancycline, sedecamycin, spectinomycin, sulbactam, sulbenicillin, temocillin, tetracycline, ticarcillin, tigemonam, tubercidine, argininsa, arbekacin, apramycin, amikacin, azithromycin, bacampicillin, cefcapene pivoxil, cefpodoxime proxetil dapsone, deoxydihydrostreptomycin dibekacin, etambutol, flumequine, guamecycline, nifurpirinol, nifurprazine, nitroxoline, glyconiazide, isoniazide, opiniazide, mupirocin, negamycin, netilmicyn, pipacycline, fortimycins, gentamycin, ibostamycin, lincomycin, micronomycin, midecamycin, miokamycin, oleandomycin, paromomycin, rosaramycin, sisomycin, streptomycin, tobramycin, trospectomycin, claritromycin, diritromycin, enviomycin, erithromycin, josamycin, midecamycin, miocamycin, rifabutine, rifamide, rifamycin, rifaxymine, rokitamycin, spiramycin, troleandromycin, viomycin, virginiamycin; p-aminosalicylic acid, benzilpenicillinic acid, acetil sulfametossipirazine, acediasulfone, 4-sulfanylamidosalicylic acid, 4,4'-sulfinyldianiline, 4'-(methylsulfamoyl)sulfanylanilide, 2-p-sulfanilylanilinoethanol, N-sulfanilyl-3,4-xylamide, p-sulfanilylanilinoethanol, p-sulfanilylbenzylamine, salazosulfadimidine, salinazid, succisulfone, sulfabenzamide, sulfacetamide, sulfachlorpiridazine, sulfachrysoidine, sulfacitine, sulfadiazine, sulfadicramide, sulfadimetoxine, sulfadoxine, sulfaetidol, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfametazine, sulfametizol, sulfamethomidine, sulfametoxazol, sulfametoxypiridazine, sulfamethyltiazol, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanylamide, sulfanylilurea, sulfaperine, sulfafenazol, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfatiazol, sulfathiourea, sulfisomidine, sulfisoxazol, sultamicillin, tiazosulfone, mafenide, clofazimine, carbomycin, clomocycline, meclocycline, metampicillin, meticillin, metronidazole, mezlocillin, moxalactam, oxytetracycline, piromidic acid, pivampicillin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, enrofloxacin, fleroxacin, grepafloxacin, lomefloxacin, norfloxacin, ofloxacin, pazufloxacin, pefloxacin, rifanpin, rufloxacin, ta-

lampicillin, trovafloxacin, tosufloxacin, sparfloxacin;

Antiviral drugs: aciclovir, amantadine, cidofovir, cytarabine, didanosine, dideoxyadenosine, edoxudine, famciclovir, floxuridine, ganciclovir, idoxuridine, indanavir, kethoxal, lamivudine, MADU, penciclovir, podophyllotoxine, ribavirine, rimantadine, saquinavir, sorivudine, stavudine, trifluridine, valacyclovir, vidarabine, xenazoic acid, zalcitabine, zidovudine;

- Inhibitors of bone reabsorption: alendronic acid, butedronic acid, etidronic acid, oxydronic acid, pamidronic acid, risedronic acid;
- Drugs for dementia: amiridine, lazabemide, mofegiline, salbeluzol, oxiracetam, ipidacrine, nebracetam, tacrine, velnacrine.

When the compounds include at least one asymmetric carbon atom, the products can be used in racemic mixture or in form of single enantiomer.

The active principle in the solid dispersions of the invention is in amorphous form. By "amorphous form" of a compound it is meant a solid form of that compound that when subjected to DSC analysis does not show the melting endothermic peak.

When the active principle is in the solid dispersions of the present invention it is characterized by a higher dissolution rate and therefore a higher bioavailability than in the non dispersed form. As it will be shown in detail in the following examples, a particularly high increase in the dissolution rate occurs when the hydrophilic polymer used in the dispersion is polyvinylpyrrolidone. Thus, the use of the polyvinylpyrrolidone as the hydrophilic polymer is particularly preferred when a very fast release of the active agent is desired.

Preferably the solid dispersions of the present invention comprise one or more nitrate active principles in amounts comprised between 5% and 60% w/w and preferably between 15% and 40% w/w and the hydrophilic polymer in amount ranging from 50% to 90%, preferably between 70% and 85% w/w.

Optionally, the solid dispersions of the present invention comprise also pharmaceutically acceptable excipients such as, for instance, wetting and solubilising agents in amount preferably ranging from 2% to 20%. Preferably the solubilising agents are surfactants, and among them most preferred are polysorbates, esters and ethers of polyethylen glycols, polihydroxylated castor oil and sodium laurylsul-

phate. The solid dispersion of the invention can be produced by using processes known in the art such as, for instance, the methods based on co-precipitation, the methods based on melting, which consist in melting together the active agent and the carrier and then cooling the melted mass, among them it is mentioned in particular "snap-cooling" where the cooling of the melted mass is carried out on stainless steel plates, "injection molding" where the molten mass is injected into a mould, hot melt extrusion where the active principles and the carrier mixture while flowing through the extruder is contemporaneously melted, homogenized and then extruded in the form of pellets, granules and other intermediates to be used for the production of tablets (the advantage of this technique is that the mixture is subjected to high temperatures just for one minute and it is therefore suitable for active agents sensible to high temperatures), "spray congealing", where cooling of the melted mass is carried out by freezing, and the methods based on solvent evaporation, consisting in dissolving the active agent and the carrier in the same solvent, or in forming an emulsion of the active agent and of the carrier in the solvent. Among these methods a technique allowing to easily and quickly obtain solid dispersions is "spray drying". An especially preferred process for the production of the solid dispersions of the invention is a spray-drying process comprising the following steps:

a) dissolving the active principle in a solution or suspension of the hydrophilic polymer;

b) spraying the mixture obtained in step (a) through the standard nozzle of a sprayer at a flow rate ranging from 5 to 60 ml/min and at a temperature of the inlet air comprised between 50°C and 130°C.

The solution or suspension of step a) can be realized in solvents such as, for instance, water, ethanol, isopropyl alcohol, methylen chloride, butanol, cyclohexane, hexane, acetone or mixture thereof. The choice of the solvent depends on the characteristics of solubility of the active agent which has to be dissolved.

The concentration of polyvinyl pyrrolidone, hydroxypropylmethylcellulose or polyethylene glycol in said solution or suspension is comprised between 1% and 10% w/v and preferably between 2.5% and 7.5% w/v.

The active principle ingredient is added to said solution or suspension in such an

amount to obtain a concentration comprised between 0.1% and 10% w/v and preferably between 0.5% and 7.5% w/v.

Optionally, at least one of the above mentioned pharmaceutically acceptable excipients can be added to the solution or suspension in such an amount as to obtain a concentration of said excipients comprised between 0.01% and 10% w/v and preferably between 0.05% and 5% w/v.

The spraying carried out in step b) is preferably carried out at a flow rate comprised between 5 and 60 ml/min and at an inlet air temperature comprised between 50°C and 130°C.

The solid dispersions of the present invention can be administrated as such, in form of powder, or used, for instance, for the production of granulates, tablets, capsules, suspensions, solutions, suppositories and aerosols.

Therefore, a further object of the present invention are pharmaceutical formulations for oral, parenteral, rectal, (trans)dermic or (trans)mucosal administration of the nitrate active principles comprising the solid dispersions of the invention.

If compared to conventional formulations, the formulations of the invention allow to improve the bioavailability and the onset of action of the nitrate active principles.

The invention will be now explained in detail by the following examples to be considered as a not limiting explanations of the invention.

EXAMPLE 1

Preparation of solid dispersions of the 4- acetylaminophenyl ester of the 4-nitroxybutanoic acid (NCX701).

A solution in methylene chloride/ethanol (90/10 v/v) including 0.8823% w/v of 4-acetylaminophenyl ester of the 4-nitroxybutanoic acid and 2.5% w/v of polyvinyl pyrrolidone K25 has been prepared. This has then been sprayed through the standard nozzle (inner diameter 1 mm) of a sprayer SD04 (Lab-Plant LTD, West Yorkshire, United Kingdom) at a flow rate of 20 ml/min while keeping an inlet hot air temperature of 60°C.

The obtained product has then been analysed by scanning calorimetry using a DSC T.A.2910 of T.A. INSTRUMENTS, with a heating interval and scanning rat of 10°C/min. under constant nitrogen flow. The obtained thermogram, reported in Figure 1, shows that the analysed product is amorphous. In fact no thermic event

is detected in the considered temperature interval and in particular in correspondance with the melting temperature of the 4-acetylaminophenyl ester of the 4 nitroxybutanoic acid, at 78°C.

EXAMPLE 2

Evaluation of the dissolution rate of 4-acetylaminophenyl ester of 4 nitroxybutanoic acid in solid dispersion

The dissolution rate of the active principle of the solid dispersion produced in Example 1 has been evaluated, in comparison with the dissolution rate of the pure active principle in micronized form with the paddle method, described in F.U.X., using the following conditions:

dissolution means: distilled water

temperature: 37°C±0.5

stirring rate: 100 r.p.m.

The quantity of active ingredient released has been evaluated by UV spectrophotometry at a wavelength of 240 nm. The following table shows the average of the results obtained from three determinations, expressed as percentage of active principle dissolved at different time intervals:

| TIME (minutes) | Micronized active principle | Solid dispersion |
|---|---|---|
| 5 | 17.8 | 100 |
| 10 | 38.8 | 100 |
| 15 | 52.1 | 100 |
| 20 | 60.7 | 100 |
| 25 | 67.5 | 100 |
| 30 | 72.4 | 100 |
| 35 | 76.4 | 100 |
| 40 | 79.7 | 100 |
| 45 | 82.6 | 100 |
| 50 | 85.2 | 100 |
| 55 | 87.3 | 100 |
| 60 | 94.9 | 100 |

As it can be observed from the table, while the active principle as such is characterized by a slow dissolution in water, when this is in the form of a solid dispersion in polyvinyl pyrrolidone its dissolution is immediate, occurring in less than five minutes.

EXAMPLE 3

Preparation of solid dispersions of 3-(nitroxymethyl)phenyl ester of 2-acetoxybenzoic acid (NCX4016)

Two solutions in methylene chloride/ethanol (90/10 v/v) having the following compositions have been prepared:

0.8823% w/v of 3-(nitroxymethyl)phenyl ester of the 2- acetoxybenzoic acid and 5% w/v of polyvinyl pyrrolidone K25;

2.1 % w/v of 3-(nitroxymethyl)phenyl ester of the 2- acetoxybenzoic acid and 5% w/p of polyvinyl pyrrolidone K25;

0.8823% w/v of 3-(nitroxymethyl)phenyl ester of the 2- acetoxybenzoic acid and 5% w/v of hydroxypropylmethylcellulose.

The solutions have then been sprayed as described in Example 1. The product obtained has been analysed by scanning calorimetry using a device described in the preceding example. The thermogram obtained, reported in Figure 2, shows that the analysed product is amorphous. In fact no thermic event is detected in the considered temperature interval and in particular in correspondance with the melting temperature of the 3-(nitroxymethyl)phenyl ester of 2-acetoxybenzoic acid, at 63.52°C.

EXAMPLE 4

Determination of the dissolution rate of NCX4016 in solid dispersion

The dissolution rate of the solid dispersion produced in the example 3 has been compared with the dissolution rate of the pure NCX4016 in micronised form using the paddle method described in F.U.X., according to the following operating conditions T = 37°C±0.5°C, stirring rate:150 rpm, dissolution means: 1% sodium lauryl sulphate solution, dissolution volume: 900 ml.

The quantity of NCX4016 released has been spectrophotometrically evaluated in continuous at a wavelength 232 nm. The following table shows the average of the results obtained from 3 determinations, expressed as percentage of active principle dissolved at different time intervals.

| TIME (minutes) | NCX4016 micronized | NCX4016 Solid dispersion 1 | NCX4016 Solid dispersion 2 | NCX4016 Solid dispersion 3 |
|---|---|---|---|---|
| 5 | 17.9 | 98.2 | 98.1 | 27.3 |
| 10 | 39.2 | 99.9 | 99.2 | 65.7 |
| 15 | 53.5 | 100 | 100 | 81.1 |
| 20 | 60.7 | 100 | 100 | 90.2 |
| 25 | 71.4 | 100 | 100 | 92.4 |
| 30 | 77 | 100 | 100 | 94.1 |
| 35 | 80.9 | 100 | 100 | 94.7 |
| 40 | 84.4 | 100 | 100 | 94.9 |
| 45 | 87 | 100 | 100 | 95.4 |
| 50 | 88.9 | 100 | 100 | 95.4 |
| 55 | 90.6 | 100 | 100 | 95.4 |
| 60 | 91.4 | 100 | 100 | 95.4 |

Also in this case, as it can be observed from the table, the dissolution rate of the active principle in all the three solid dispersions is higher than that of the active principle in pure form. Moreover, when the active principle is dispersed in polyvinyl pyrrolidone, the increase in the dissolution rate is remarkably high and an almost immediate release is observed.

EXAMPLE 5

Evaluation of the dissolution rate of 3-(nitroxymethyl)phenyl ester of the 2-acetoxybenzoic acid (NCX4016) in solid dispersion under condition of supersaturation

Three samples of microspheres have been exactly weighed so as to have a con-

tent of nitroaspirine of 30 mg. This quantity corresponds to about 4 times the solubility in water of the active principle.

The dissolution rate of the active principle from the above mentioned 3 solid dispersions has been compared with the dissolution rate of the pure active principle in micronized form, with the paddle method, described in F.U.X. using the following conditions:

dissolution means: distilled water

temperature: 37°c±0.5

stirring rate: 100 r.p.m.

volume = 900 ml

The quantity of NCX 4016 released has been evaluated spectrophotometrically in continuous at a wavelength 232 nm.

The samples have been taken by means of a peristaltic pump at 5 minutes intervals and for the total time of one hour.

The following table shows the average of the results obtained from three determinations, expressed as percentage of dissolved active principle at different time intervals:

| TIME (minutes) | Micronized active principle | Solid dispersion 2 |
|---|---|---|
| 5 | n.r.[a] | 55.1 |
| 10 | n.r.[a] | 54.3 |
| 15 | n.r.[a] | 51.8 |
| 20 | n.r.[a] | 48.7 |
| 25 | n.r. | 46.9 |
| 30 | Nr.[a] | 44.7 |
| 35 | n.r.[a] | 42.8 |
| 40 | n.r.[a] | 40.8 |
| 45 | n.r.[a] | 38.6 |
| 50 | n.r.[a] | 37.3 |
| 55 | n.r.[a] | 35.7 |
| 60 | n.r.[a] | 34.3 |

a: spectrophotometrically not detectable

The quantity of active agent NCX4016 dissolved after 5 minutes is about twice the solubility of the active ingredient in the dissolution means.

EXAMPLE 6

Preparation of solid dispersions of HCT 1026 (2-fluoro-α-methyl[1.1'biphenyl]4-acetic acid-4nitrooxy butyl ester

Two solutions in methylene chloride/ethanol (90/10 v/v) with the following compositions have been prepared:

HCT 1026 0.44% w/v; polyvinyl pyrrolidone K 30 2.5% w/v

HCT 1026 0.88% w/v; polyvinyl pyrrolidone K 30 2.5% w/v

The solutions have then been sprayed under the same conditions used in Example 1.

EXAMPLE 7

Evaluation of the dissolution rate of the HTC1026 in solid dispersion

The dissolution rate of the HCT 1026 from the solid dispersion 1 has been evaluated, in comparison with the dissolution rate of the pure active ingredient, with the paddle method described in F.U.X. In detail, 50 mg of the solid dispersion 1 and 7.5 mg of pure active ingredient are placed in a thermostatic container at 37°C±0.5°C in 900 ml of distilled water including 1% w/v of SDS and kept under stirring at 150 rpm. The quantity of HCT 1026 passed into the solution is continuously spectrophotometrically determined in continuous at a wavelength of 245 nm.

In the following table the average of the results obtained from three determinations is reported, expressed as percentage of active principle dissolved at different time intervals:

| TIME (minutes) | Pure HCT 1026 | Solid dispersion 1 |
|---|---|---|
| 5 | 5.84 | 81.04 |
| 10 | 16.74 | 84.74 |
| 15 | 23.6 | 85.2 |
| 20 | 29.84 | 86.13 |
| 25 | 32.78 | 85.67 |
| 30 | 37.92 | 85.85 |
| 35 | 42.57 | 86.31 |
| 40 | 47.46 | 86.68 |
| 45 | 54.94 | 86.78 |
| 50 | 58.98 | 86.78 |
| 55 | 58.98 | 87.42 |
| 60 | 64.72 | 87.79 |

The results obtained show also in this case that when the active agent is in solid dispersion in polyvinyl pyrrolidone its dissolution speed is much higher than the one of the active agent in non dispersed form, and the release of more than 80% of the active principle is observed in less than 5 minutes.

EXAMPLE 8

Preparation of solid dispersions of NCX 1022 (hydroxycortisone 21-[(4'-nitroxymethyl)benzoate]

A solution of methylene chloride/ethanol (90/10 v/v) including 0.44% w/v of NCX 1022 and 2.5% w/v of polyvinyl pyrrolidone K25 has been prepared. It has then been sprayed through the standard nozzle (1 mm inner diameter) of a sprayer SD04 (Lab-Plant LTD, West Yorkshire, United Kingdom) with a flow rate of 20 ml/min keeping a temperature of the inlet hot air of 60°C.

The product obtained has then been analyzed through scanning calorimetry by using the device described in the preceding examples. The thermogram obtained, reported in Figure 3, shows that the analysed product is amorphous and degrades at a temperature lower than 200°C. In fact no thermic event is detected in the considered interval of temperature and in particular in correspondance with the melting temperature of the NCX 1022.

EXAMPLE 9

Determination of the dissolution speed of the solid dispersion of NCX 1022

The dissolution rate of the active ingredient from the solid dispersion produced in Example 6 has been compared with the dissolution rate of the pure active ingredient, using the paddle method described in F.U.X. In detail, 40 mg of the solid dispersion or 5 mg of pure NCX 1022 have been placed in a thermostated container at 37°C±0.5°C in 500 ml of distilled water including 1% w/v of Tween 80 and kept under stirring at 100 rpm. The quantity of NCX 1022 dissolved has been spectrophotometrically determined in continuous at a wavelength of 240 nm.

The following table shows the average of the results obtained from three determinations, expressed as percentage of ingredient dissolved at different time intervals:

| TIME (minutes) | Micronized active principle | Solid dispersion |
|---|---|---|
| 5 | 4.05 | 45.56 |
| 10 | 3.91 | 49.73 |
| 15 | 3.86 | 50.36 |
| 20 | 3.81 | 49.90 |
| 25 | 3.91 | 48.84 |
| 30 | 3.77 | 47.18 |
| 35 | 3.91 | 45.60 |
| 40 | 3.77 | 43.71 |
| 45 | 4.09 | 41.93 |
| 50 | 4.33 | 40.2 |
| 55 | 4.23 | 38.82 |
| 60 | 4.32 | 37.18 |

The results obtained show that, even if the solubility of the pure active principle almost null, with a solubilisation of only 4.3% within one hour, when this is in form of a solid dispersion in polyvinyl pyrrolidone its dissolution rate and therefore its apparent solubility remarkably increase and it is possible to obtain the release of 50% of active ingredient in less than 15 minutes.

CLAIMS

1. Solid dispersions comprising at least one nitrate active ingredient and on hydrophilic polymer chosen among cellulose ether, polyvinyl pyrrolidone, polyethylene glycol.

2. Dispersions according to claim 1 wherein said polymer is polyvinyl pyrrolidone .

3. Dispersions according to claim 1 wherein said cellulose ether is hydroxypropylmethylcellulose and it has a molecular weight such that the viscosity at 20°C of a 2% solution in water is lower than 50 cps.

4. Dispersions according to claim 1 wherein polyvinyl pyrrolidone has an average molecular weight comprised between the molecular weight of polyvinyl pyrrolidone K17 and the molecular weight of polyvinyl pyrrolidone K30.

5. Dispersions according to claim 1 wherein polyethylene glycol has an average molecular weight higher than or equal to the molecular weight of polyethylene glycol 1000.

6. Dispersions according to claim 1 wherein said active ingredient is contained in amounts ranging from 10% to 50% w/w and said hydrophilic polymer is contained in amounts ranging from 50% to 90%.

7. Dispersions according to claim 6 wherein the amount of said active ingredient is between 15% and 40% w/w.

8. Dispersions according to claim 6 wherein the amount of said hydrophilic polymer is between 60% and 85%.

9. Dispersions according to claim 1 further comprising pharmaceutically acceptable excipients.

10. Dispersions according to claim 9 wherein said excipients are contained amounts comprised between 2% and 20%.

11. Dispersions according to claim 9 wherein said pharmaceutically acceptable excipients are chosen from the group consisting of wetting and solubilising agents.

12. Dispersions according to claim 11 wherein said solubilising agents are surfactants.

13. Dispersions according to claim 12 wherein said surfactants are chosen from the group comprising polysorbates, esters and ethers of polyethylene glycols, polyhydroxylated castor oil and sodiumlauryl sulphate.

14. Pharmaceutical formulations for oral, rectal, parenteral, transcutaneous, transmucosal administration of active principles comprising the solid dispersions according to claims 1 to 13.

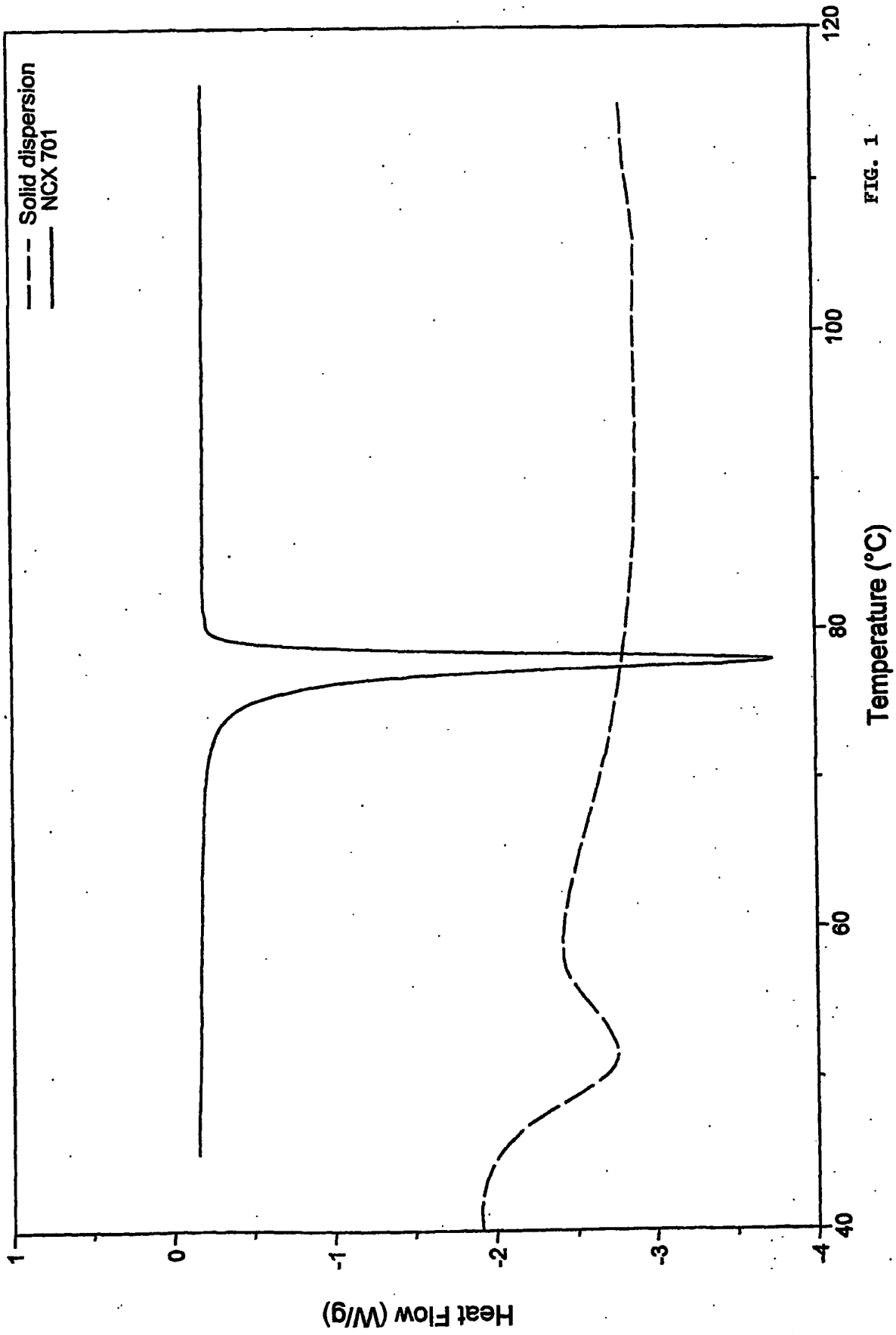

Solid dispersion
NCX 701
Heat Flow (W/g)
1
0
-1
-2
-3
-4
40
60
80
100
120
Temperature (°C)

FIG. 1

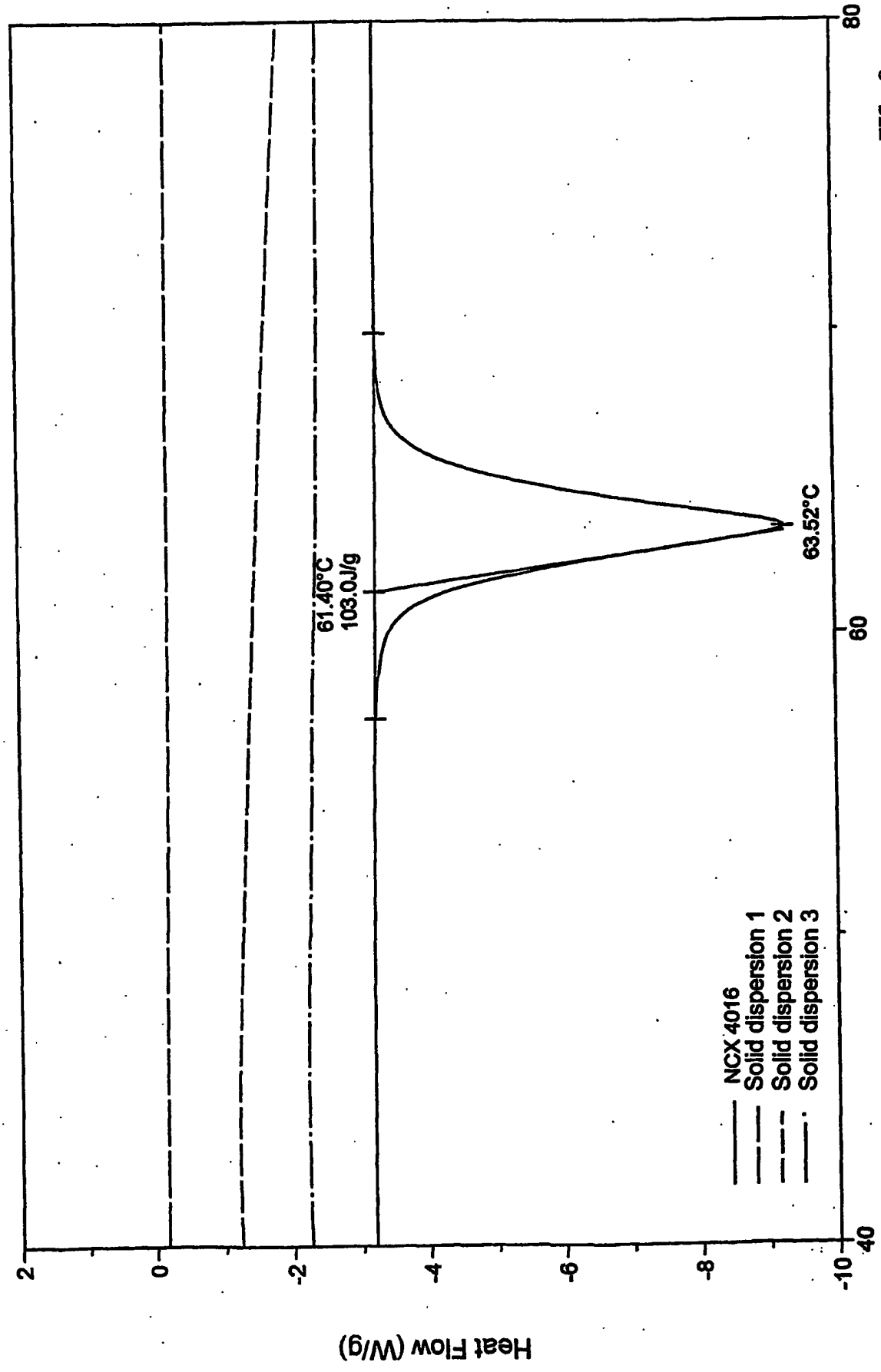

Heat Flow (W/g)
2
0
-2
-4
-6
-8
-10
40
60
80
Temperature (°C)
61.40°C
103.0J/g
63.52°C
NCX 4016
Solid dispersion 1
Solid dispersion 2
Solid dispersion 3

FIG. 2

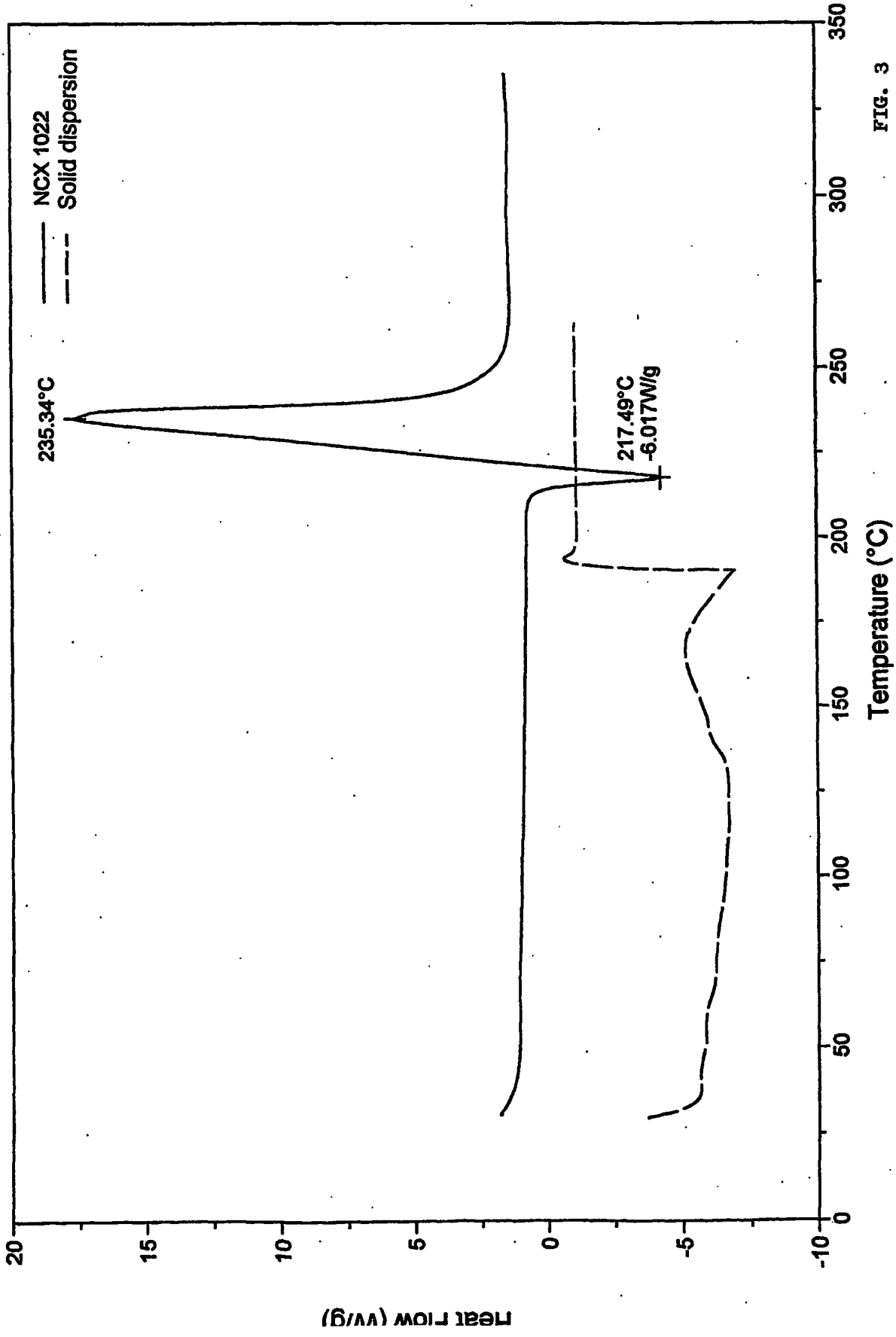

NCX 1022
Solid dispersion
235.34°C
217.49°C
-6.017W/g
Heat Flow (W/g)
Temperature (°C)
20
15
10
5
0
-5
-10
0
50
100
150
200
250
300
350

FIG. 3

# INTERNATIONAL SEARCH REPORT

I Application No
PCT/EP 01/14967

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | MINGHETTI, P.; ET AL.: "Application of solubility parameter in nitroflurbiprofen topical semisolid formulations" PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON CONTROLLED RELEASE OF BIOACTIVE MATERIALS 27TH, 7 - 13 July 2000, pages 936-937, XP002199487 Paris (FR) | 1,5,9,14 |
| Y | page 936; example 2; table 1 | 1 |
| P,Y | WO 01 15677 A (ALCON LABORATORIES) 8 March 2001 (2001-03-08) claims 1,7,10,11 page 10, line 6 - line 17 page 14, line 1 - line 8 | 1 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 21 May 2002 | 06/06/2002 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Ventura Amat, A |

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

nal Application No
PCT/EP 01/14967

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 0115677 A | 08-03-2001 | AU 6917400 A | 26-03-2001 |
| | | WO 0115677 A2 | 08-03-2001 |

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International Bureau

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(11) International Publication Number: **WO 99/00361**

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(71) Applicant *(for all designated States except US)*: NICOX S.A. [FR/FR]; 45, avenue Kléber, F–75116 Paris (FR).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I–20052 Monza (IT).

(74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni, 2, I–20129 Milano (IT).

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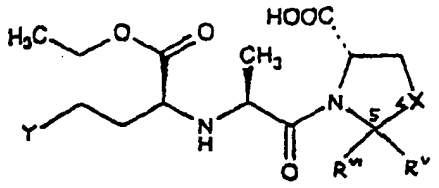
(54) Title: ACE–INHIBITOR NITRIC SALTS

(57) Abstract

Ace–inhibitor nitric salts having formulae (I), (II), (III).



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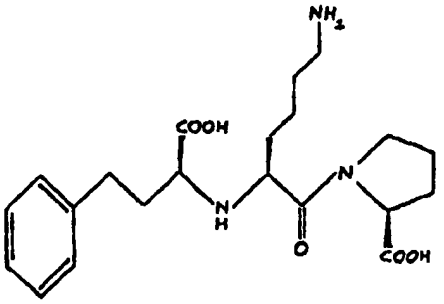

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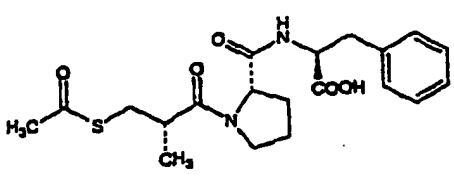

(III)

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# ACE-INHIBITOR NITRIC SALTS

*********

The present invention relates to products having an antihypertensive activity combined with a platelet-antiaggregating activity, and pharmaceutical compositions thereof.

In particular, it relates to products having an improved antihypertensive activity and fewer side effecs, in particular in the bronchi, compared to the products currently being marketed as antihypertensive agents. The antihypertensive activity is combined with a platelet-antiaggregating activity.

Antihypertensive agents are known in the art. Particularly known are ACE inhibitors, which represent a first-choice pharmacological measure in the treatment of cardiovascular diseases such as hypertension, angina, myocardial ischaemia, congestive heart failure, and others. ACE inhibitors act on the renin-angiotensin system which releases angiotensin II, one of the most effective hypertensive agents known. More precisely, these drugs inhibit the activity of the angiotensin converting enzyme, a carboxypeptidase which is mostly present in lungs, kidneys, and vessels. The action of this enzyme is not specific. It inactivates plasma bradykinin,

which possesses a vasodilatatory activity. and also helps diuresis and, in particular, natriuresis. In other terms, plasma bradykinin possesses opposite effects compared to those of angiotensin II. Therefore, ACE inhibitors prevent formation of angiotensine II and, at the same time, degradation of bradykinin. Hence, ACE inhibitors certainly represent one of the most significant pharmacological innovation of the past few decades.

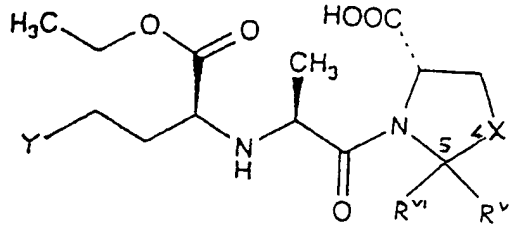
However, the administration of ACE inhibitors is often (about 20 to 30% of the cases) accompanied by side effects in the respiratory system, such as cough, dyspnea, broncho-constriction. Furthermore, these drugs show a rather limited therapeutic profile, for example they have no platelet-anti-aggregating activity, so that, in the above cardiovascular treatments, they are often associated with other drugs having an antiaggregating activity. For example, in the treatment of myocardial infarction and prevention of relapses, it is essential to use a multiple cardiovascular therapy including, among others, the association of an antihypertensive with an antiaggregating agent.

It was felt the need for drugs with a better therapeutic profile and fewer side effects, in particular, at the respiratory system, for example the bronchi.

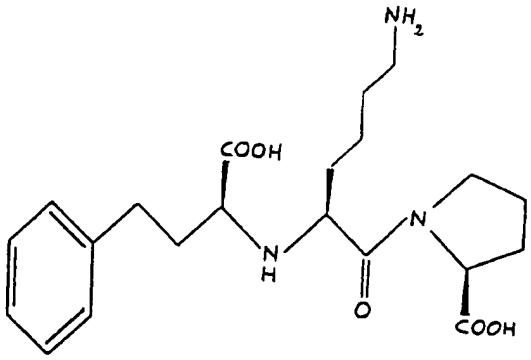
The Applicant has unexpectedly and surprisingly found a

specific class of ACE-inhibitor salts characterised by the fact that they possess, compared to other salts of the same compounds, a better antihypertensive activity and have fewer side effects in the bronchi.

An object of the present invention is, therefore, the nitric salts of ACE inhibitors having the following formulas:



(I)



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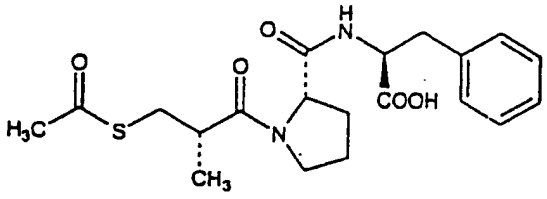
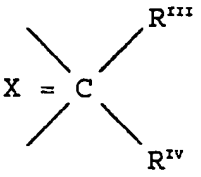


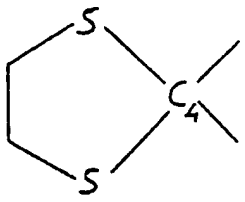
(III)

in formula (I)  or $N-CH_3$;

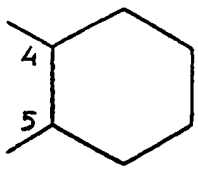
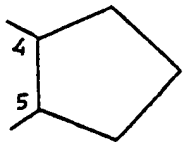
Y = $CH_3$, phenyl;

$R^{III}$ = H,

$R^{III}$ together with $R^{IV}$ forms the following ring in the carbon at position 4

 (IVa);

$R^{III}$ together with $R^{V}$ (carbons at positions 4 and 5) forms the cyclohexane or cyclopentane rings

 (IIIa)  (IIIb);

$R^{IV}$ = H, or $R^{IV}$ forms with $R^{III}$ ring (IVa);

$R^{V}$ = H, or a free valence, or $R^{V}$ forms with $R^{III}$ rings (IIIa) or (IIIb);

$R^{VI}$ = H, or a single bond -O when $R^{V}$ is a free valence so as to form a ketone group with the carbon atom at position 5.

The preferred nitrate salts of formula (I) include:

when X = C ($R^{III}$) ($R^{IV}$) as above defined, Y = phenyl, $R^{III}$ = $R^{IV}$

= $R^V$ = $R^{VI}$ = H, the residue of Enalapril;

as in Enalapril but with $R^{III}$ which, together with $R^{IV}$, forms ring (IVa), the residue of Spirapril;

as in Enalapril but with $R^{III}$ which, together with $R^V$, forms ring (IIIb), the residue of Ramipril;

as in Enalapril but with Y = $CH_3$ and $R^{III}$ which, together with $R^V$, forms ring (IIIa), the residue of Perindopril;

as in Enalapril, but with X = N-$CH_3$, $R^V$ is a free valence and $R^{VI}$ = -O so as to form with carbon atom $C_5$ a ketone group, the residue of Imidapril.

The compounds of the classes of the invention, which are the precursors of the salts, are used as optically-active single isomers or as mixtures thereof or in the form of racemates.

The precursor of class II is known as Lisinopril, that of class III is known as Alacepril. The precursors are prepared according to the methods described in "The Mercx Index, Ed. 12", herein incorporated by reference.

The salts of the present invention are prepared according to the following method. The substance to be salified is dissolved in an organic solvent, not containing in the molecule free hydroxyl groups, and then a stoichiometric amount of concentrated nitric acid is added. The salt is recovered by filtration and washed several times with a

solvent, for example that used in the reaction. Polar organic solvents are preferred, such as , for example, acetonitrile, ethyl acetate, and others.

It has surprisingly been found that the compounds of the present invention improve, compared to the same substances and ACE salts generally, the pharmacological profile of the above ACE inhibitors and, additionally, exhibit a more favourable general and regional tolerability.

The compounds of the present invention can be used as cardiovascular drugs, in particular in the treatnent of hypertension, angina, myocardial ischaemia, congestive heart failure.

The salts of the present invention are formulated in the correspomding pharmaceutical compositions according to the methods well known to those skilled in the art, which are, for example, described in Remington's Pharmaceutical Sciences, Ed. 15.

The examples below are meant to describe the invention and should not be understood as a limitation of same.

EXAMPLE 1

Synthesis of (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline (Enalapril), and obtainement of the nitrate salt in acetonitrile

A mixture of ethyl-2-oxo-4-phenylbutyrate (2.1 g) and

L-alanyl-L-proline (0.4 g) in ethanol/water 1/1 was treated slowly at room temperature with a solution of sodium cyanoborohydride (0.4 g) in ethanol/water 1/1.

At the end of the reaction, the product was absorbed on a strong acid ion exchange resin and eluted with an aqueous solution containing 2% (v/v) of pyridine. The fractions which contained the product were lyophilised to obtain the crude compound. Chromatography then allowed isolation of the desired isomer (-) practically pure (0.24 g).

The isomer was then dissolved in acetonitrile and treated, maintaining the reactor in an ice bath, with a stoichiometric amount of concentrated nitric acid dissolved in acetonitrile. After cooling and filtration, the solid was washed with cold acetonitrile and a 97%-pure (HPLC: high pressure liquid chromatography) Enalapril nitric salt was recovered. A 99%-pure (HPLC) salt could be obtained by crystallisation from acetonitrile.

EXAMPLE 2

Synthesis of Enalapril, and obtainement of the nitrate salt in ethyl acetate

A mixture of ethyl-2-oxo-4-phenylbutyrate (15 g), L-alanyl-L-proline (9 g), molecular sieves 3A° (40 g) and Raney nickel (10.8 g) in ethanol (300 ml) was hydrogenated at room temperature and at a pressure of about 3 atm. up to the

hydrogen is not consumed any more. After filtration of the undissolved substance (washing well with ethanol, the solvent was evaporated under vacuunm to obtain a mixture of diastereoisomers formed of 85% by the expected product (by HPLC). The obtained product was dissolved in a mixture made up of 200 ml of water and 70 ml of methyl acetate. By keeping the solution under stirring, the pH was adjusted to 8.6 with 50% NaOH. The organic phase was separated and the aqueous phase was thoroughly washed with ethyl acetate (3 x 50 ml). The aqueous phase was adjusted to pH 4.3 with hydrochloric acid, saturated with sodium chloride and then extracted with ethyl acetate (4 x 100 ml). After drying with sodium sulphate and evaporating the solvent off under vacuum, the residue was dissolved in ethyl acetate maintaining the reactor in an ice bath, and salified by treating with a stoichiometric amount of concentrated nitric acid. After stirring for two hours, it was cooled, filtered, washed with ethyl acetate and recrystallised from acetonitrile to obtain 12.5 g of nitric salt of the isomer (-), about 99%-pure (by HPLC).

EXAMPLE 3

Acute toxicity

A group of 10 mice (weight 15 to 25 g) received a single oral dose of 100 mg/Kg. All the animals survived during the observation period (14 days). No toxicity symptom was

observed.

EXAMPLE 4

Antihypertensive activity

The antihypertensive activity of the nitrate salts of the compounds of the invention was determined in accordance with the method of Laubie et al., J. Cardiovasc. Pharmacol. 6, 1076, 1984. N° 6 rats weighing about 200 to 250 g were used per experimental group. Four groups were formed, which were intraperitoneally treated respectively as shown below:

- Enalapril maleate 100 μg/Kg
- Enalapril maleate 300 μg/Kg
- Enalapril nitrate 100 μg/kg
- Enalapril nitrate 300 μg/kg

The doses are referred to the amount of Enalapril (cation) in the salt. The antihypertensive response was evaluated as per-cent inhibition of the hypertension induced by the administration of a dose of 100 μg/Kg i.v. of angiotensin I as described in the above article.

The results are shown in Table I

TABLE I

| COMPOUND | DOSE (μg/Kg/i.p.) | Inhibition % for angiotensin-I-induced hypertension |
|---|---|---|

| | | |
|---|---|---|
| Enalapril maleate | 100 | 18 |
| Enalapril maleate | 300 | 55 |
| Enalapril nitrate | 100 | 35 |
| Enalapril nitrate | 300 | 67 |

EXAMPLE 5

Pharmacological effects of the salts of the invention on bronchial spasm induced by administration of substance P

Activity was evaluated measuring the strengthening of bronchial spasm induced by substance P, determined in accordance with the method of Subissi et al., Br. J. Pharmacol. 100, 502-6, 1990. The model described by Subissi is predictive of bronchial side effects due to the administration of ACE inhibitors.

Four groups (6 animals/group) of female Guinea pigs weighing about 300 to 400 g were anaesthetised with ethyl urethane (200 mg/Kg) under artificial pressure at constant positive pressure. The compounds were administered intraperitoneally 30 minutes before substance P. The salt doses administered were the same as in Example 4. The changes in tidal air were then measured in accordance wuth the method of Konzett, Arch. Exp. Pathol. Pharmacol. 195, 71, 1940, before and after the administration of substance P (200 μg/Kg), with or without the test salts, i.e. Enalapril maleate and nitrate.

The results are shown in Table II

As seen from the data, Enalapril nitrate possessed a better respiratory profile than Enalapril maleate at both tested doses.

TABLE II

| COMPOUND | DOSE (μg/Kg/i.p.) | Tidal air change % in bronchial spasm induced by substance P |
|---|---|---|
| Enalapril maleate | 100 | + 16 |
| Enalapril maleate | 300 | + 28 |
| Enalapril nitrate | 100 | - 5 |
| Enalapril nitrate | 300 | - 7 |

EXAMPLE 6

Platelet-antiaggregating activity

The in-vivo model described by Pinon et al., J. Pharm. Methods 12, 79-84, 1984, was used.

Two groups of 6 rats each, weighing about 200 to 250 g, were treated with an oral dose of 10 mg/Kg/die of Enalapril maleate or nitrate respectively (the dose is referred to the amount of Enalapril cation in the salt) for five days, while a third group acted as a control group. About 18 hours before the last treatment, the animals were fasted. One hour after

this treatment the animals were anaesthetised with 10% ethyl urethane (1 g/Kg intraperitoneally) and the left jugular vein and the right carotid artery were cannulated. Collagen (type 6, Sigma) was then administered intravenously at a dose of 2 mg/Kg. Three minutes later two blood samples, A and B, were collected from the carotid artery of each animal.

1.6 ml of EDTA/formalin buffer (24 mM tetrasodium EDTA, 1.3 mM $KH_2PO_4$, 13.4 mM $Na_2HPO_4$) was added to the first sample (sample A) containing 0.4 ml of blood.

The second blood sample (sample B) had the same volume as the previous sample (0.4 ml of blood) but, instead of the buffer, 1.6 ml of a saline solution (physiological NaCl solution) was added.

The samples were then transferred into 5-ml test tubes and allowed to stand at room temperature for 15 minutes.

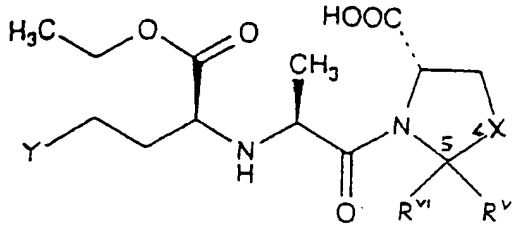
A microscope platelet count was then performed. The platelet count in samples B and A represent the total number of platelets and the total number of aggregated platelets respectively. The results shown in Table III are expressed as a % of platelet aggregation and are referred to the % value obtained in the control group.

TABLE III

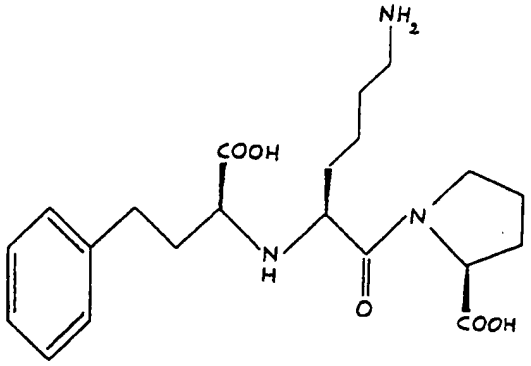
| COMPOUND | DOSE/die (mg/Kg/os) | Antiaggregating activity % |
|---|---|---|
| Enalapril maleate | 10 | 5 |
| Enalapril nitrate | 10 | 58 |

## CLAIMS

1. Nitric salts of ACE inhibitors having the following formulas:



(I)



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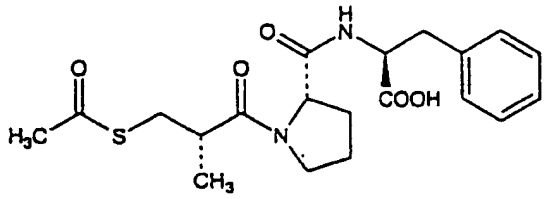
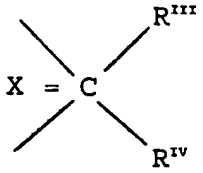


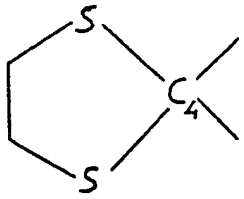
(III)

in formula (I)  or $N-CH_3$

Y = $CH_3$, phenil;

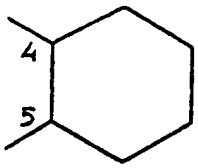
$R^{III}$ = H,

$R^{III}$ together with $R^{IV}$ forms the following ring in the carbon at position 4

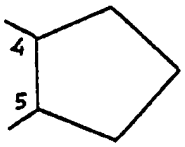



(IVa);

$R^{III}$ together with $R^{V}$ (carbons at positions 4 and 5) forms the cyclohexane or cyclopentane rings




(IIIa)




(IIIb);

$R^{IV}$ = H, or $R^{IV}$ forms with $R^{III}$ ring (IVa);

$R^{V}$ = H, or a free valence or $R^{V}$ forms with $R^{III}$ rings (IIIa) or (IIIb);

$R^{VI}$ = H, or a single bond -O when $R^{V}$ is a free valence so as to form a ketone group with the carbon atom at position 5.

2. Nitric salts according to claim 1, wherein, in formula (I), X = C ($R^{III}$) ($R^{IV}$), Y = phenyl, $R^{III}$ = $R^{IV}$ = $R^{V}$ = $R^{VI}$ = H, the residue of Enalapril;

as in Enalapril but with $R^{III}$ which, together with $R^{IV}$,

forms ring (IVa), the residue of Spirapril;

as in Enalapril but with $R^{III}$ which, together with $R^{V}$, forms ring (IIIb), the residue of Ramipril;

as in Enalapril but with Y = $CH_3$ and $R^{III}$ which, together with $R^{V}$, forms ring (IIIa), the residue of Perindopril;

as in Enalapril, but with X = N-$CH_3$, $R^{V}$ is a free valence and $R^{VI}$ = -O so as to form with carbon atom $C_5$ a ketone group, the residue of Imidapril.

3. Nitric salts according to claim 2, wherein, in formula (I), X = C ($R^{III}$) ($R^{IV}$), Y = phenyl, $R^{III}$ = $R^{IV}$ = $R^{V}$ = $R^{VI}$ = H, the residue of Enalapril.

4. Nitric salts according to claims 1 to 3, used for the preparation of pharmaceutical compositions as anti-hypertensive agents.

5. Nitric salts according to claims 1 to 3, used for the preparation of pharmaceutical compositions as antiaggregating agents.

6. Nitric salts according to claims 1 to 3, used for the preparation of pharmaceutical compositions as anti-hypertensive and antiaggregating agents.

7. Nitric salts according to claims 1 to 3, used for the preparation of pharmaceutical compositions as cardio-vascular agents for the treatment of hypertension, angina, myocardial ischaemia, congestive heart failure.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/03946

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D207/16 C07K5/068 A61K31/40 A61K38/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A,P | US 5 645 839 A (CHOBANIAN ARAM ET AL)<br>8 July 1997<br>see the whole document<br>--- | 1-7 |
| A | CHEMICAL ABSTRACTS, vol. 115, no. 15,<br>14 October 1991<br>Columbus, Ohio, US;<br>abstract no. 149997,<br>XP002085266<br>see abstract<br>& R.J. KATZ ET AL.: CIRCULATION,<br>vol. 83, no. 4, 1991, pages 1271-1277,<br>---<br>-/-- | 1-7 |

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|---|---|
| 20 November 1998 | 04/12/1998 |

| Name and mailing address of the ISA | Authorized officer |
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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | CHEMICAL ABSTRACTS, vol. 116, no. 19, 11 May 1992 Columbus, Ohio, US; abstract no. 187771, XP002085267 see abstract & ALI F. HAJJ-ALI ET AL.: EUR. J. PHARMACOL., vol. 212, no. 2-3, 1992, pages 279-281, --- | 1-7 |
| A | CHEMICAL ABSTRACTS, vol. 119, no. 5, 2 August 1993 Columbus, Ohio, US; abstract no. 40531, XP002085268 see abstract & F.J. HOCK ET AL.: BIOL. NITRIC OXIDE, PROC. INT. MEET., 2ND , vol. 1, 1991, pages 279-281, --- | 1-7 |
| A | CHEMICAL ABSTRACTS, vol. 124, no. 13, 25 March 1996 Columbus, Ohio, US; abstract no. 164763, XP002085269 see abstract & G.J. DUSTING ET AL.: AM. J. CARDIOL., vol. 76, no. 15, 1995, pages 24e-7e, --- | 1-7 |
| A | CHEMICAL ABSTRACTS, vol. 125, no. 11, 9 September 1996 Columbus, Ohio, US; abstract no. 132132, XP002085270 see abstract & J.R. RUMBLE ET AL.: J. HYPERTENS., vol. 14, no. 5, 1996, pages 601-607, --- | 1-7 |
| A,P | CHEMICAL ABSTRACTS, vol. 128, no. 4, 26 January 1998 Columbus, Ohio, US; abstract no. 30226, XP002085271 see abstract & H. WATANABE ET AL.: AM. HEART J., vol. 134, no. 4, 1997, pages 614-621, --- | 1-7 |
| A,P | CHEMICAL ABSTRACTS, vol. 128, no. 21, 25 May 1998 Columbus, Ohio, US; abstract no. 253007, XP002085272 see abstract & CN 1 141 771 A (JIA LI, PEOP. REP. CHINA) ----- | 1-7 |

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/03946

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 5645839 A | 08-07-1997 | NONE | |

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(71) Applicant *(for all designated States except US)*: JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: JANS, Eugeen [BE/BE]; Rodekruislaan 3, B-2450 Meerhout (BE). SMANS, Guido, Franciscus [BE/BE]; Molenpad 60, B-2275 Lille (BE). GILIS, Paul, Marie, Victor [BE/BE]; Schransdriesstraat 14, B-2340 Beerse (BE).

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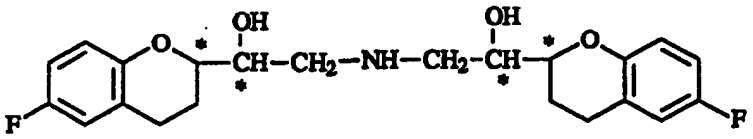
(54) Title: COMPOSITIONS CONTAINING MICRONIZED NEBIVOLOL

(57) Abstract

The present invention relates to pharmaceutical compositions containing as active ingredient micronized nebivolol of formula (I) and ways of preparing said compositions.

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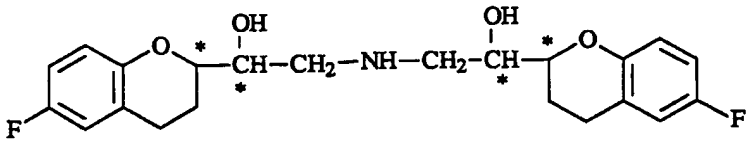
# Compositions containing micronized nebivolol

The present invention relates to pharmaceutical compositions comprising as active ingredient a micronized form of solid nebivolol or a pharmaceutically acceptable acid addition salt thereof and ways of preparing said compositions.

Nebivolol is the generic name of (±)-[R*[S*[S*-(S*)]]]-α,α'-[iminobis(methylene)bis-[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol]. The general structure of nebivolol is shown as formula (I). The structure of formula (I) has four stereogenic centers which are each indicated with an asterisk.



(I),

Nebivolol is a mixture of equal amounts of 2 enantiomers having respectively the SRRR- and the RSSS-configuration. The SRRR-configuration is referred to as $SR_3$-nebivolol (d-nebivolol) and the RSSS-configuration is referred to as $RS_3$-nebivolol (l-nebivolol). $SR_3$-nebivolol is a potent and selective $\beta_1$-adrenergic antagonist both *in vitro* and *in vivo*. Nebivolol can be distinguished from other β-adrenergic antagonists because it acutely lowers blood pressure in spontaneously hypertensive rats, decreases total peripheral vascular resistance and augments stroke volume in anaesthetised dogs. These haemodynamic effects are largely attributable to $RS_3$-nebivolol. It was also discovered that $RS_3$-nebivolol is a potentiator for a series of antihypertensive agents such as atenolol, propanolol, prazosin, hydralazine and, interestingly, also its own enantiomer, i.e. $SR_3$-nebivolol. Several clinical trials have also demonstrated the therapeutic potential of nebivolol as a $\beta_1$-selective beta-blocker and antihypertensive agent.

EP-0,145,067 generally describes 2,2'-iminobisethanol derivatives useful for the treatment and /or prevention of disorders of the coronary vascular system. EP-0,334,429 describes [iminobismethylene]bis[3,4-dihydro-2H-1-benzopyran-2-methanol]derivatives including nebivolol.

Nebivolol may be prepared according to the procedures described in EP-0,145,067 and more specifically in EP-0,334,429. Nebivolol has basic properties and may be converted into its pharmaceutically acceptable acid addition salt forms by treatment with appropriate acids. Appropriate acids are, for example, inorganic acids, such as hydrohalic acid, e.g. hydrochloric, hydrobromic and the like, and sulfuric acid, nitric acid, phosphoric acid; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzene-sulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. The acid addition salt that is preferred in this invention is the hydrochloride acid addition salt.

Pharmaceutical compositions according to the present invention are solid or semi-solid pharmaceutical compositions. Interesting solid pharmaceutical compositions are, for instance, powders, pills, capsules, tablets and the like. The term "semi-solid pharmaceutical composition" refers to pharmaceutical compositions substantially consisting of a dispersion of solid active ingredient in a (highly) viscous formulating agent. Interesting semi-solid pharmaceutical compositions are, for instance, suppositories, creams, gels, ointments and the like.

Interesting solid pharmaceutical compition is a single-unit dosage form, i.e. a non-multi-particulate dosage form.

The solid dosage form that is preferred within the present invention is a tablet. The person skilled in the art has to take into account the characteristics of tablets while searching for a composition. Specific characteristics of tablets are shape, disintegration time, and particularly hardness.

Oral administration constitutes the generally preferred route for administration of pharmaceuticals since this route is particularly convenient and acceptable to patients. However, preparing a solid dosage form for oral administration having all the correct characteristics sometimes forms a serious challenge for a person skilled in the art of preparing pharmaceutical compositions. In order for a substance to be effective, it has to reach appropriate concentrations in the bloodstream of the patient within an acceptable time after intake. In other words the substance has to have an acceptable bioavailability.

A very important factor influencing the bioavailability of substances after oral intake is the dissolution, i.e. the rate of dissolving of the substance, particularly in gastric fluid. It is recognized that the dissolution for the solid dosage form of the present invention should amount to at least 75% in 45 minutes in 0.1N HCl at a temperature of 37°C. Said dissolution is measured according to the test procedure described in example 5 hereinafter. Said test procedure is analogous to the test procedures mentioned in official pharmacopoeias, e.g. the U.S. Pharmacopoeia XXII.

The person skilled in the art of developing pharmaceutical compositions is faced with the problem of making a solid dosage form suitable for oral administration so that the compound of formula (I) has an acceptable dissolution. Moreover, said person skilled in the art is bound by other limiting conditions. The pharmaceutical composition developed by him will be prepared on industrial scale and will have to satisfy the requirements of internal and external quality control.

Oral administration of nebivolol hydrochloride is impeded by the poor dissolution when in a normal crystalline form. In the course of the investigations towards improving the bioavailability of nebivolol hydrochloride, the product was micronized. Unfortunately, as can be seen from example 3, the dissolution of micronized nebivolol hydrochloride is even worse than nebivolol hydrochloride in normal crystalline form.

Unexpectedly however, it was found that when nebivolol hydrochloride in micronized form is formulated in a composition with art-known formulating agents as described hereinunder it has an appropriate dissolution and meets internal and external quality control requirements.

Hence, the present invention provides a particularly advantageous formulation of nebivolol hydrochloride. There is thus provided according to the invention a pharmaceutical composition having an appropriate dissolution, more particular a pharmaceutical composition for oral administration comprising a solid dosage form including nebivolol hydrochloride in micronized form.

Micronized forms of nebivolol hydrochloride may be prepared by micronization techniques known in the art, e.g. by milling in appropriate mills and sieving through appropriate sieves.

The specific area of said micronized material should at least amount to about 23 x $10^3$ $cm^2/g$ (2.3 x $10^3$ $m^2/kg$), preferably the specific area should amount to more than 25 x $10^3$ $cm^2/g$ (2.5 x $10^3$ $m^2/kg$), more preferably more than 28 x $10^3$ $cm^2/g$ (2.8 x $10^3$ $m^2/kg$), and most preferably more than 31 x $10^3$ $cm^2/g$ (3.1 x $10^3$ $m^2/kg$).

According to this invention the characteristics of the micronized nebivolol hydrochloride are as follows. At most 50% of the particles may have a diameter larger than 10 μm, i.e. the $DL_{50}$ has a maximum value of 10 μm. Preferably the $DL_{50}$ should amount to less than 8 μm. At most 10% of the particles may have a diameter larger than 20 μm, i.e. the $DL_{10}$ has a maximum value of 20 μm. Preferably the $DL_{10}$ should amount to less than 18 μm.

Compositions according to the present invention will preferably comprise pharmaceutically acceptable carriers and excipients, such as fillers e.g. lactose, sucrose, mannitol, maize starch, microcrystalline cellulose or calcium hydrogen phosphate; lubricants e.g. stearic acid, polyethylene glycol, magnesium stearate, talc or silica; disintegrants e.g. rice, potato or maize starch, sodium starch glycolate or croscarmellose sodium (i.e. sodium carboxymethylcellulose) ; binding agents e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropylmethylcellulose and wetting agents e.g. sodium dioctylsulfosuccinate and Polysorbates.

Interesting fillers are lactose, sucrose or microcrystalline cellulose; preferably lactose and microcrystalline cellulose. Interesting lubricants are stearic acid, polyethylene glycol, hydrogenated vegetable oil, sodium stearyl fumarate or magnesium stearate, preferably magnesium stearate. Interesting disintegrants are rice, potato or maize starch, preferably croscarmellose sodium. Preferred binding agent is hydroxypropylmethylcellulose.

It was found that polysorbates were the wetting agents of choice. Interesting wetting agents are Polysorbate 20 (Tween 20®), Polysorbate 40 (Tween 40®), Polysorbate 60 (Tween 60®), Polysorbate 80 (Tween 80®), Polysorbate 65 (Tween 65®), Polysorbate 85 (Tween 85®). More interesting wetting agents are Polysorbate 20, Polysorbate 40, Polysorbate 60, Polysorbate 80. Preferred wetting agent is Polysorbate 80.

Interesting compositions comprise by weight based on the total weight of the composition:

| | | |
|---|---|---|
| nebivolol hydrochloride | : | from 1% to 4% |
| fillers | : | from 60% to 90% |
| disintegrants | : | from 3% to 10% |
| binding agents | : | from 0.5% to 5% |
| wetting agents | : | from 0.1% to 1.0 % |

More interesting compositions comprise by weight based on the total weight of the composition.

| | | |
|---|---|---|
| nebivolol hydrochloride | : | from 1% to 4% |
| fillers | : | from 75% to 85% |
| disintegrants | : | from 4% to 8% |
| binding agents | : | from 1% to 3% |
| lubricants | : | from 0.4% to 0.9% |
| wetting agents | : | from 0.1% to 0.8% |

Preferred compositions comprise by weight based on the total weight of the composition.

| | | |
|---|---|---|
| nebivolol hydrochloride | : | from 2% to 3% |
| lactose | : | from 55% to 65% |
| maize starch | : | from 15% to 25% |
| croscarmellose sodium | : | from 5% to 7% |
| hydroxypropyl methylcellulose | : | from 1% to 3% |
| polysorbate | : | from 0.1% to 0.5% |
| magnesium stearate | : | from 0.4% to 0.6% |

For the preparation of compositions according to the invention micronized nebivolol hydrochloride is blended with suitable excipients and granulated. Preferably nebivolol hydrochloride will be granulated with the filler or fillers before admixture of the other excipients. Most preferably the fillers employed will be lactose and maize starch.

The ratio (w/w) of wetting agent / nebivolol hydrochloride is an important factor. In order to achieve a good dissolution the active ingredient has to be sufficiently wetted. On the other hand when the amount of wetting agent is too high in the composition, the resulting tablets do not have the appropriate hardness and consequently said tablets are not suitable for industrial production.

The ratio (w/w) of wetting agent / nebivolol hydrochloride may vary between about 0.025 and 0.5. Said ratio may preferably range from about 0.025 to about 0.3. More preferably said ratio ranges from about 0.04 to about 0.25. Most preferably said ratio ranges from about 0.06 to 0.1.

Tablets according to this invention may be right circular cylinders or may have a rod-like shape, the end surfaces of which may be flat or convex and the edges of which may be levelled. Said tablets may have lines or break-marks and may bear a symbol or other markings.

A further aspect of the invention provides a method of treating a patient suffering from conditions associated with coronary disorders and hypertension which comprises oral administration of a pharmaceutical composition comprising a solid dosage form comprising micronized nebivolol hydrochloride.

It will be appreciated that the precise therapeutic dose of the active ingredient will depend in the age and condition of the patient and the nature of the condition to be treated and will be at the ultimate discretion of the attendant physician.

However, in general effective doses for the treatment of conditions associated with coronary disorders and hypertension, will lie in the range of about 0.1 to about 50 mg, most preferably about 1 to about 10 mg, for example about 5 mg of the active ingredient per unit dose which could be administered in single or divided doses, for example, 1 to 4 times per day.

Experimental Part

Example 1 : Preparation of nebivolol hydrochloride

(±)-[2R*[1S*,5S*(S*)]] + [2R*[1S*,5R*(R*)]]-α,α'[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] (142g) was converted into the hydrochloric acid salt in ethanol (1000ml). The crystals were filtered off and crystallized from ethanol. The second fraction of the crystallization was recrystallized from ethanol, yielding 10.3g (6.6%) of (±)-[2R*[1S*,5S*(S*)]] -α,α'[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] hydrochloride; mp. 224.9°C nebivolol hydrochloride (crystalline compound 1).

Example 2 : Micronization of nebivolol hydrochloride

A quantity of 11 kg of nebivolol hydrochloride was micronized using a Air Classifying Mill with a milling disc equipped with stones. The working speed is optimal at 13,500 revolutions per minute. When the particles are small enough they are taken up with the air stream and led to a wind sieve, where they are collected, yielding micronized compound 1.

Example 3 : dissolution test

| | specific area $m^2/kg$ | dissolution after 60 minutes |
|---|---|---|
| crystalline compound 1 | $0.226 \times 10^3$ | 28.1 % |
| micronized compound 1 | $3.012 \times 10^3$ | 17.4 % |

Example 4 : Preparation of tablets containing compound 1

*Composition of the final tablet :*

| | | |
|---|---|---|
| nebivolol hydrochloride : | 5.45 mg | 2.40 % |
| lactose: | 141.75 mg | 61.6 % |
| maize starch : | 46.00 mg | 20.0 % |
| croscarmellose sodium | 13.80 mg | 6.00 % |
| colloidal anhydrous silica : | 0.60 mg | 0.26 % |
| magnesium stearate | 1.15 mg | 0.50 % |
| hydroxypropyl methylcellulose (Hypromellose) 2910 15 cps (*): | 4.60 mg | 2.00 % |
| polysorbate 80 : | 0.46 mg | 0.20 % |
| microcrystalline cellulose : | 16.10 mg | 7.00 % |

(*) Hypromellose is the British Approved Name as well as the recommended International Nonproprietary Name for hydroxypropyl methylcellulose. The classes of hydroxypropyl methylcellulose are distinguished by a four digit code, here 2910. The first two digits represent the approximate percentage composition of methoxyl groups, and the third and fourth digits the approximate percentage composition of hydroxypropyl groups. The indication "15 cps" refers to the viscosity of 15 centipoise (15 mPa.s) of a 2 % solution measured at 20 °C.

*Preparation of the binder solution*

92 g of hydroxypropyl methylcellulose 2910 15 cps and 9.2 g polysorbate 80 were dissolved in 1,840 g demineralized water under magnetic stirring at a temperature of 90°C.

*Preparation of the granulate*

109 g nebivolol hydrochloride, 138 g croscarmellose sodium, 2,835 g lactose and 920 g of maize starch are mixed in a fluidized-bed granulator under a working pressure of 5-6 bar. The inlet air temperature is 60°C. The mixing process is continued up until the outlet air temperature has reached a temperature of 30°C. Subsequently, the binder solution is sprayed onto the powder mixture. After the spraying the granulate is dried with an inlet air temperature being 75°C.

*Preparation of the compression mixture*

The dried granulate, 322 g microcrystalline cellulose, 138 g croscarmellose sodium, 13 g colloidal anhydrous silica and magnesium stearate are sieved through a stainless-steel frame sieve (mesh : 0.95 mm) and are mixed in a planetary powder mixer until a homogeneous mixture is obtained.

*Preparation of the tablets*

From the above compression mixture tablets of 230 mg are prepared using a rotary tablet press.

Example 5 : Dissolution test

*Preparation of the standard solution.*

Approximately 54.5 mg of nebivolol hydrochloride was weighed accurately in a 50 ml volumetric flask. Said quantity of nebivolol hydrochloride was dissolved in methanol and diluted to volume (50 ml) with methanol.

*Preparation of the reference solution.*

A quantity of 5 ml of the standard solution (see above) was pipetted into a 500 ml volumetric flask. A placebo tablet was added as well as 300 ml hydrochloric acid 0.1 N. This solution was heated to 37 °C and shaken mechanically for 30 minutes. The solution was further diluted to a volume of 500 ml with hydrochloric acid 0.1 N. Subsequently the solution was filtered through a 15 µm filter.

*Preparation of the sample solution.*

A tablet comprising micronized nebivolol hydrochloride (prepared as described in example 4) was placed into a dissolution vessel of the Paddle apparatus as described in the European Pharmacopoeia with a rotation speed set at 50 ± 2 revolutions per minute and the dissolution medium being hydrochloric acid 0.1 N and a fixed temperature of 37 °C ± 0.5 °C.

*Measurement*

After 45 minutes of stirring in the dissolution vessel a sample of 6 ml was withdrawn from the dissolution vessel and filtered through a 15 µm reagent filter. The absorbance of the sample was measured using a spectrophotometer (after a second filtration through a 0.2 µm filter) at the maximum near 280 nm, in a 10 mm-cell against a "blank solution" consisting of hydrochloric acid 0.1 N.

*Calculation*

$$A_S\ corr. = \frac{54.5.A_s}{W_s}$$

Where $A_S$ = measured absorbance of the 'reference solution'.

$W_S$ = weighed quantity, in mg, of nebivolol hydrochloride reference material

$$\%\ \text{dissolved} = \frac{A_{45}}{A_s corr.}.100$$

Where $A_{45}$ = measured absorbance of the 45-minutes sample

Tablets as prepared in Example 4 showed a dissolution of 75 %, i.e. 75% dissolved, after 45 minutes.

Example 6 : Comparison of dissolution of tablets comprising crystalline versus micronized nebivolol

| Tablet 1 | Tablet 2 | |
|---|---|---|
| compound 1 crystalline | compound 1 microfine | 5.45 mg |
| polysorbate 80 | polysorbate 80 | 2.30 mg |
| hydroxypropyl methylcellulose 2910 15 cps | hydroxypropyl methylcellulose 2910 15 cps | 4.60 mg |
| lactose | lactose | 139.91 mg |
| maize starch | maize starch | 46.00 mg |
| acdisol | acdisol | 13.80 mg |
| microcrystalline cellulose | microcrystalline cellulose | 16.10 mg |
| colloidal anhydrous silica | colloidal anhydrous silica | 0.69 mg |
| magnesium stearate | magnesium stearate | 1.15 mg |

The dissolution rates fo the tablets were measured using an analogous procedure as described in Example 5. The tablets were placed in a dissolution vessel of the Paddle apparatus with a rotation speed set at about 100 revolutions per minute, the dissolution medium being artificial gastric juice and the temperature fixed at 37 °C. The dissolution rate of the tablet comprising crystalline nebivolol (tablet 1) amounted to less than 50 % after 45 minutes, while the dissolution rate of the tablet comprising micronized nebivolol (tablet 2) amounted to more than 75 % after 45 minutes.

Claims

1. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient nebivolol or a pharmaceutically acceptable salt thereof characterized in that the active ingredient is in a micronized solid form.

2. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutical composition is a solid pharmaceutical composition.

3. A pharmaceutical composition as claimed in claim 1 or 2, wherein the active ingredient is a micronized form of nebivolol hydrochloride.

4. A pharmaceutical composition as claimed in claim 3, wherein the micronized form of nebivolol hydrochloride has a specific surface area of at least 23 x $10^3$ $cm^2/g$ (2.3 x $10^3$ $m^2/kg$).

5. A pharmaceutical composition as claimed in claim 3, wherein said pharmaceutical composition comprises 1 to 4 % of a micronized form of nebivolol hydrochloride.

6. A pharmaceutical composition as claimed in claim 3, wherein said pharmaceutical composition further comprises a Polysorbate as a wetting agent and wherein the ratio (w/w) of Polysorbate to nebivolol hydrochloride ranges from 0.025 to 0.5.

7. A pharmaceutical composition as claimed in claim 2, wherein said pharmaceutical composition is a tablet.

8. A pharmaceutical composition as claimed in claim 3, wherein said pharmaceutical composition is a tablet substantially having the following composition :

| | |
|---|---|
| nebivolol hydrochloride : | 2.40 % |
| lactose: | 61.6 % |
| maize starch : | 20.0 % |
| croscarmellose sodium | 6.00 % |
| colloidal anhydrous silica : | 0.26 % |
| magnesium stearate | 0.50 % |
| Hypromellose 2910 15 cps : | 2.00 % |
| Polysorbate 80 : | 0.20 % |
| microcrystalline cellulose : | 7.00 % |

9. A tablet as claimed in claim 7, characterized in that it has a dissolution of 75% after 45 minutes.

10. A micronized form of nebivolol hydrochloride having a specific area of at least $23 \times 10^3$ $cm^2/g$.

# INTERNATIONAL SEARCH REPORT

Internatic Application No
PCT/EP 95/00489

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/35 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | EP,A,0 145 067 (JANSSEN PHARMACEUTICA N.V.) 19 June 1985<br>cited in the application<br>see claims 1,4-8<br>see page 9, line 25 - line 27<br>see page 10, line 12 - line 13<br>see page 41, line 9 - line 34<br>see page 42, line 1 | 1-10 |
| A | EP,A,0 334 429 (JANSSEN PHARMACEUTICA N.V.) 27 September 1989<br>cited in the application<br>see claims 1-3,11,13<br>see page 5, line 45 - line 47<br>see page 6, line 6 - line 7 | 1-10 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati. . Application No
PCT/EP 95/00489

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| EP-A-0145067 | 19-06-85 | AU-B- | 573658 | 16-06-88 |
| | | AU-A- | 3632684 | 13-06-85 |
| | | JP-C- | 1630034 | 20-12-91 |
| | | JP-B- | 2050114 | 01-11-90 |
| | | JP-A- | 60132977 | 16-07-85 |
| | | SU-A- | 1428199 | 30-09-88 |
| | | US-A- | 4654362 | 31-03-87 |
| EP-A-0334429 | 27-09-89 | AU-A- | 3074289 | 28-09-89 |
| | | ES-T- | 2052881 | 16-07-94 |
| | | HK-A- | 123594 | 18-11-94 |
| | | IL-A- | 89691 | 12-04-94 |
| | | JP-A- | 1283220 | 14-11-89 |
| | | JP-B- | 6037487 | 18-05-94 |
| | | PT-B- | 90095 | 30-11-94 |